EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

BIOVAIL LABORATORIES, INC. a corporation of Barbados	:	
	:	Civil No. 02-7119
Plaintiff,	:	
	:	Judge: Anita B. Brody
vs.	:	
TORPHARM, INC., a Canadian Corporation,	:	
Defendant.	:	

DEFENDANT, COUNTERCLAIM PLAINTIFF, TORPHARM, INC.'s SECOND AMENDED ANSWER TO AMENDED COMPLAINT FOR PATENT INFRINGEMENT, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS

Defendant, responds to the amended complaint as follows:

JURISDICTION, VENUE, AND PARTIES

1. Admitted.

2. Defendant is without sufficient information and belief as to the truth of the allegations of paragraph 2 and therefore denies those allegations.

3. Admitted.

4. Admitted.

5. No response is necessary as the allegation requires a conclusion of law.

6. Admitted with respect to TorPharm's registered agent. No response is necessary as to either personal jurisdiction or venue since these are conclusions of law.

BIOVAIL'S NEW DRUG APPLICATION AND BIOVAIL'S RIGHTS UNDER THE '791 PATENT

7. Admitted that U.S. Patent No. 5,529,791 ("the '791 patent") issued on June 25, 1996. Regarding the remaining allegations, Defendant is without sufficient information and belief as to the truth of the remaining allegations of paragraph 7 and therefore denies those allegations.

8. Admitted that U.S. Patent No. 5,288,505 ("the '505 patent") issued on February 22, 1994. Regarding the remaining allegations, Defendant is without sufficient information and belief as to the truth of the remaining allegations of paragraph 8 and therefore denies those allegations.

9. Defendant is without sufficient information and belief as to the truth of the allegations of paragraph 9 and therefore denies those allegations.

10. Admitted.

TORPHARM'S ACT OF PATENT INFRINGEMENT UNDER 35 U.S.C. §271(e)(2)

11. Admitted that TorPharm advised Plaintiff by means of a letter dated July 16, 2002, that TorPharm had filed Abbreviated New Drug Application ("ANDA") No. 76-395 to market a generic version of Diltiazem HCl Capsules Type TZ (Diltiazem Hydrochloride Extended-Release Capsules USP) 120 mg, 180 mg, 240 mg, 300 mg and 360 mg, and that it had certified to the FDA, pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification"), that the '791 patent "will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted."

Denied the TorPharm's letter failed to provide "a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed", as is required

by 21 U.S.C. §355(j)(2)(B)(i) and (ii), and that it alleged only in conclusory terms that its proposed ANDA product would not infringe the '791 patent. TorPharm's letter set out a detailed factual and legal basis in support of its certification. Denied in all other respects.

12. Admitted.

13. Denied.

COUNT 1 - Infringement Of The '791 Patent Under 35 U.S.C. §271)e)(2)

14. TorPharm incorporates its responses to paragraphs 1-13 herein.

15. Denied.

COUNT II - Infringement of the '505 Patent Under 28 U.S.C. §2201 and 35 U.S.C. §271(a)

16. TorPharm incorporates its responses to paragraphs 1-15 herein.

17. This is a conclusion of law to which no response is necessary. Subject to the foregoing, TorPharm submits that Biovail has no right under the Declaratory Judgment Act to seek a ruling with respect to the '505 patent as the patent is not listed in the Orange Book as mandated by 21 CFR §314.53(b). The Orange Book requires that an NDA holder/applicant list all relevant patents for which a reasonable claim of patent infringement could be brought if a generic company such as TorPharm manufactured the product.

18. Denied.

19. Denied.

20. Denied.

21. Denied.

22. Denied except admitted that TorPharm's counsel did not provide a copy of TorPharm's ANDA when TorPharm's counsel learned that Biovail breached their agreement for production of the ANDA. Biovail originally requested the ANDA to determine issues of potential infringement of the '791 patent and never informed TorPharm's counsel of the '505 patent. Biovail had only requested the ANDA with respect to determining issues of potential infringement related to the '791 patent which is listed in the Orange Book and for which TorPharm made a paragraph IV patent certification. The '505 patent is not listed in the Orange Book. Thus, Biovail's counsel improperly attempted to obtain TorPharm's ANDA for purposes beyond the '791 patent without any notice to TorPharm's counsel in violation of the parties' agreement and in contempt of the Protective Order entered in a parallel case in the Northern District of Illinois.

23. Denied.

COUNT III - Infringement of the '505 Patent Under 35 U.S.C. §271(e)(2)

24. TorPharm incorporates its responses to paragraphs 1-23 herein.

25. Denied.

AFFIRMATIVE DEFENSES

A. The '791 and '505 patents are not infringed.

B. Plaintiff has failed to state a claim upon which relief may be granted.

C. The Court lacks jurisdiction to decide issues related to the '505 patent as the '505 patent is not listed in the Orange Book.

D. Defendant reserves the right to assert further affirmative defenses and counterclaims, including but not limited to invalidity of the patents in suit, unenforceability of the patents in suit, and for anti-trust violations for the institution of a sham suit.

E. The '791 and '505 patents are invalid for failure to meet the conditions of patentability of 35 U.S.C. § 102 as being anticipated by the prior art and § 103 as being obvious over the prior art.

F. The '791 and '505 patents do not meet one or more of the conditions of patentability specified in 35 U.S.C. § 112 and are invalid, void and unenforceable against TorPharm for any or all of the following reasons:

(a) The specifications thereof are incomplete, vague and indefinite and do not contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which they pertain, or with which they are most nearly connected, to make and use the same; and/or

(b) The claims of the '791 and '505 patents are vague, indefinite, and overbroad and fail to particularly point out and distinctly claim the subject matter of the alleged invention; and/or

(c) The claims of the '791 and '505 patents are inoperable and overbroad and would force one of ordinary skill in the art attempting to practice those claims, to perform undue experimentation; and/or

(d) The claims of the '791 and '505 patents are overbroad and are not enabled by the specifications.

G. The '791 and '505 patents are invalid for failure to meet the conditions of patentability of 35 U.S.C. § 101, as said patents lack utility and are inoperable due to overbreadth.

WHEREFORE, Defendant requests that this Honorable Court:

a. Deny Plaintiff all requested relief and dismiss the Complaint with prejudice.

b. Order that the effective date of the approval of Defendant's application (ANDA) is immediate under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), upon a statement by the FDA that it is otherwise ready to approve the ANDA.

c. Declare that the '791 and '505 patents are not infringed.

d. Defendant further requests that this Court award it its attorneys' fees, costs and all other relief this Court deems just.

e. Declare that the '791 and '505 patents are invalid as being anticipated by and/or obvious over the prior art.

f. Declare that the '791 and '505 patents are invalid as lacking enablement, being indefinite, being inoperable due to overbreadth and/or lacking utility.

g. Declare that the '791 and '505 patents are invalid due to the overbreadth of the claims thereof.

COUNTERCLAIMS

1. Defendant, TorPharm, incorporates by reference herein its Answer and Affirmative Defenses to the Amended Complaint.

THE PARTIES

2. TorPharm, Inc. is a Canadian corporation having a place of business at 50 Steinway Blvd., Toronto, Ontario, M9W 6Y3, Canada. TorPharm is engaged in the business of manufacturing, marketing and filing for regulatory approvals of generic versions of pharmaceuticals to enable low cost alternative pharmaceuticals to be provided to consumers.

3. On information and belief, Biovail Laboratories, Inc. ("Biovail") is a corporation organized and existing under the laws of Barbados and has a place of business in Carolina, Puerto Rico.

4. On information and belief, Biovail is the owner of the '791 and '505 patents.

JURISDICTION AND VENUE

5. These counterclaims constitute an action for a declaratory judgment under 28 U.S.C. §§ 2201 and 2202, and arise under the Patent Laws of the United States, Title 35, United States Code.

6. This Court has jurisdiction of these counterclaims under 28 U.S.C. §§ 1331 and 1338(a) and Patent Laws of the United States, Title 35, United States Code.

7. In the Complaint, Biovail alleges that it is the owner of the '791 and '505 patents and alleges that TorPharm has infringed the '791 and '505 patents.

8. The '791 patent is listed in the Orange Book pursuant to 21 CFR § 314.53(b).

9. TorPharm made a paragraph IV certification to the '791 patent as part of TorPharm's ANDA submission.

10. The '505 patent is not listed in the Orange Book.

11. Since the '505 patent is not listed in the Orange Book, TorPharm was not required to make any certification to the '505 patent as part of its ANDA submission.

12. Under the Food, Drug and Cosmetic Act ("the FDCA"), the Food and Drug Administration ("the FDA") is responsible for determining whether a generic version of a drug product is safe and effective and should be approved for sale to the public under 21 U.S.C. § 355(a) by a generic manufacturer such as TorPharm.

13. Under the Hatch-Waxman Act, a generic pharmaceutical manufacturer such as TorPharm seeking FDA approval to market a generic version of a patented drug such as Diltiazem HCl Capsules Type TZ may submit an Abbreviated New Drug Application ("ANDA") under 21 U.S.C. § 355(j), also known as Section 505(j) of the FDCA.

14. TorPharm has submitted an ANDA seeking FDA approval to market generic Diltiazem HCl Capsules Type TZ as Plaintiff admitted in its Amended Complaint.

15. Under 21 U.S.C. § 355(j)(6)(A)(i), the Secretary of Health and Human Services (HHS) shall publish and make available to the public a list in alphabetical order of each drug which has been approved for safety and effectiveness (known as the Approved Drug Products With Therapeutic Equivalence Evaluation, also known as the "Orange Book").

16. Diltiazem Hydrochloride is listed in the Orange Book.

17. The Secretary is required to update the list every thirty days under 21 U.S.C. § 355(j)(6)(A)(ii).

18. When an innovator such as the Plaintiff receives a patent covering a pharmaceutical composition or method of using the pharmaceutical composition, the innovator is required to send the information to the Secretary of Health and Human Services so that the patent may be listed in the Orange Book.

19. Thus, when a generic manufacturer such as TorPharm is interested in marketing a generic drug, it would look to the Orange Book for the listed patent information, to determine: which if any patents exist on a particular pharmaceutical product; when those patents expire; whether the proposed product would infringe any of the listed patents; or whether the listed may be invalid.

20. Under 21 U.S.C. § 355(j)(6)(A)(iii), when patent information (e.g., patent number, for each drug for which a reasonable claim of patent infringement could be made) is submitted concerning a drug on the list to be published by the Secretary, the Secretary shall include such information in the Orange Book.

21. Under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), found in 21 C.F.R. § 314.94(a)(1-2)(vi), as interpreted by the FDA, an entity submitting an ANDA for a generic producer (such as TorPharm) must make a certification to the FDA only for patents listed in the Orange Book.

22. Thus, TorPharm and other generic manufacturers rely and have relied upon the patents listed in the Orange Book in considering whether to file and in filing ANDAs.

23. A patent innovator must list in the Orange Book, drug substance patents (ingredient), drug product patents (formulation and composition) and method of use patents. Process of making the product may not be submitted to the FDA. 21 CFR 314.53(b).

24. When an applicant such as TorPharm submits an ANDA to the FDA, the applicant must certify one of four things under 21 U.S.C. § 355(j)(2)(A)(vii)(l)-(IV) (also known as Section 505(j)(2)(A) of the FDCA):

(I) that such patent information has not been filed by the patentee (also known as a "paragraph I Certification"); or

(II) that such patent has expired (also known as a "paragraph II Certification"); or

(III) the date on which the patent will expire (also known as a "paragraph III Certification"); or

(IV) that such patent is invalid or that it will not be infringed by the manufacture, use or sale of the new drug for which the ANDA is submitted (also known as a "paragraph IC Certification").

25. Inclusion of a paragraph IV certification in an ANDA, however, is deemed an act of infringement under the laws of the United States. 35 U.S.C.A. § 271(e)(2)(A).

26. Regarding an ANDA containing a paragraph IV certification, the statute states, "It shall be an act of infringement" to submit an application under 21 U.S.C. § 355(j) "for a drug claimed in a patent ... if the purposes of such submission is to obtain approval ... to engage in the commercial manufacture, use, or sale of [the] drug ... before the expiration of [the] patent."

27. If an ANDA contains a paragraph I or a paragraph II certification as defined above, and all applicable scientific and regulatory requirements have been met, FDA approval of the ANDA is effective immediately under 21 U.S.C. § 355(j)(4)(A), (B)(i).

28. If an ANDA contains a paragraph III certification as defined in ¶18(III) above, and all applicable scientific and regulatory requirements have been met, approval is effective on the patent expiration date stated in the certification under 21 U.S.C. § 355(j)(4)(A), (B)(iv).

29. Under 21 U.S.C. § 355(j)(4)(B)(iii), if the ANDA contains a paragraph IV certification as defined above, and all applicable scientific and regulatory requirements have been met, approval of the ANDA "shall be made effective immediately" unless the patent owner brings an action for infringement under 35 U.S.C.A. § 271(e)(2)(A) within forth-five (45) days of receiving the notice required by 21 U.S.C. § 355(j)(2)(B).

30. The Hatch-Waxman Act further provides that, when a patent owner brings a section 271(e)(2)(A) infringement action, the FDA must suspend approval of the ANDA for a maximum of thirty (30) months, or until the court rules, whichever is earlier as explained below.

31. Under 21 U.S.C. § 355(j)(4)(B)(iii)(I)-(III), 35 U.S.C. § 271(e)(4)(A), the suspension continues, and the FDA cannot approve and ANDA, until the earliest of three dates:

(i) if before the expiration of the thirty month period, the court decides that the patent is invalid or not infringed, the date of the court's decision;

(ii) if before the expiration of the thirty month period, the court decides that the patent has been infringed, the date that the patent expires; or

(iii) if before the expiration of the thirty month period, the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug, until the court decides that such patent is invalid or not infringed, the date of the court decision.

32. The manufacture, use, or sale of a patented drug is not an act of infringement, to the extent it is necessary for the preparation and submission of an ANDA. 35 U.S.C. § 271(e)(1).

33. The Hatch-Waxman Act provides under 35 U.S.C. §271(e)(1), generally that "[i]t shall not be an act of infringement to make, use, or sell a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs."

34. As evidenced by the Complaint and this pleading in response thereto, Plaintiff submits the there is an actual controversy existing between the parties with respect to the alleged infringement of the '791 and '505 patents.

COUNT I

35. TorPharm incorporates by reference herein paragraphs 1-34 of its counterclaims.

36. The '791 patent is not infringed.

COUNT II

37. TorPharm incorporates by reference herein, paragraphs1-36 of its counterclaims.

38. The '505 patent is not infringed.

COUNT III

39. Biovail has failed to state a claim upon which relief may be granted concerning the '505 patent since the '505 patent is not listed in the Orange Book and TorPharm has not provided any patent certification with respect to the '505 patent.

40. The fact that the '505 patent is not listed in the Orange Book clearly indicates that Biovail does not have any "reasonable belief" as required by the statute that the manufacture of TorPharm's proposed product would infringe the '505 patent.

41. Biovail's claim is an attempt to unduly delay this case and maintain its monopoly power in the marketplace for the product.

COUNT IV

42. TorPharm incorporates by reference herein, paragraphs 1-41 of its counterclaims.

43. TorPharm hereby requests a declaration that the '791 patent is invalid for failure to meet all the conditions and requirements for patentability specified in Title 35 of the U.S. Code § 102 as being anticipated by the prior art.

COUNT V

44. TorPharm incorporates by reference herein, paragraphs 1-43 of its counterclaims.

45. TorPharm hereby requests a declaration that the '791 patent is invalid for failure to meet all the conditions and requirements for patentability specified in Title 35 of the U.S. Code § 103 as being obvious over the prior art.

COUNT VI

46. TorPharm incorporates by reference herein, paragraphs 1-45 of its counterclaims.

47. TorPharm hereby requests a declaration that the '505 patent is invalid for failure to meet all the conditions and requirements for patentability specified in Title 35 of the U.S. Code § 102.

COUNT VII

48. TorPharm incorporates by reference herein, paragraphs 1-47 of its counterclaims.

49. TorPharm hereby requests a declaration that the '505 patent is invalid for failure to meet all the conditions and requirements for patentability specified in Title 35 of the U.S. Code § 103.

COUNT VIII

50. TorPharm incorporates by reference herein, paragraphs 1-49 of its counterclaims.

51. TorPharm hereby requests a declaration that the '791 patent is invalid against TorPharm for failure to meet one or more of the conditions of patentability specified in Title 35 of the U.S. Code § 112 for any or all of the following reasons:

(a) The specification thereof is incomplete, vague and indefinite and does not contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same; and/or

(b) The claims of the '791 patent are vague, indefinite, and overbroad and fail to particularly point out and distinctly claim the subject matter of the alleged invention; and/or

(c) The claims of the '791 patent are inoperable and overbroad and would force one of ordinary skill in the art attempting to practice those claims, to perform undue experimentation; and/or

(d) The claims of the '791 patent are overbroad and are not enabled by the specifications.

COUNT IX

52. TorPharm incorporates by reference herein, paragraphs 1-51 of its counterclaims.

53. TorPharm hereby requests a declaration that the '505 patent is invalid against TorPharm for failure to meet one or more of the conditions of patentability specified in Title 35 of the U.S. Code § 112 for any or all of the following reasons:

(a) The specification thereof is incomplete, vague and indefinite and does not contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same; and/or

(b) The claims of the '505 patent are vague, indefinite, and overbroad and fail to particularly point out and distinctly claim the subject matter of the alleged invention; and/or

(c) The claims of the '505 patent are inoperable and overbroad and would force one of ordinary skill in the art attempting to practice those claims, to perform undue experimentation; and/or

(d) The claims of the '505 patent are overbroad and are not enabled by the specifications.

COUNT X

54. TorPharm incorporates by reference herein, paragraphs 1-53 of its counterclaims.

55. TorPharm hereby requests a declaration that the '791 patent is invalid for lack of utility and/or inoperability due to overbreadth under Title 35 of the U.S. Code § 101.

COUNT XI

56. TorPharm incorporates by reference herein, paragraphs 1-55 of its counterclaims.

57. TorPharm hereby requests a declaration that the '505 patent is invalid for lack of utility and/or inoperability due to overbreadth under Title 35 of the U.S. Code § 101.

COUNT XII

58. TorPharm incorporates by reference herein, paragraphs 1-57 of its counterclaims.

59. This Counterclaim is brought for monopolization pursuant to § 2 of the Sherman Act, 15 U.S.C. §2.

60. Jurisdiction is predicated upon 28 U.S.C. §§ 1131 and 1337.

61. Upon information and belief, the product market relevant to this action is the market for Tiazac and its generic equivalents ("the market for Tiazac"). Upon information and belief, Tiazac is a prescription drug used to treat high blood pressure and angina. Upon information and belief, prescriptions for Tiazac can only be filled with Tiazac or its generic equivalent. Upon information and belief, patients who have been prescribed Tiazac and their pharmacists can only fill prescriptions for Tiazac with

Tiazac or its generic equivalent. Upon information and belief, the relevant geographic market is the United States.

62. Upon information and belief, pricing of Tiazac and its generic equivalents remains high due to Biovail's enforcement of the '505 and '791 patents. If the '505 and '791 patents were not in force, TorPharm intends and is prepared to bring a generic version of Tiazac to market. TorPharm has in the past brought other generic pharmaceuticals to market upon approval of ANDAs by the FDA. TorPharm has the capacity to enter the Tiazac market by virtue of manufacturing arrangements it has in place with affiliated companies and contractors and therefore would be positioned to begin sale of a generic equivalent to Tiazac immediately upon receiving approval of their ANDA, which approval, upon information and belief, is imminent.

63. Upon information and belief, Biovail has enforced the invalid '505 and '791 patents through litigation they knew, or should have known, to be baseless for the purpose of injuring potential competitors and monopolizing or attempting to monopolize the relevant market described above, and have successfully obtained monopoly power in preventing and restraining competition in said market.

64. Upon information and belief, Biovail instituted the baseless litigation for the purpose of obtaining a 30 month stay pursuant to the Hatch-Waxman Act and, in fact, obtained said stay even though it knew, or should have known, that the litigation was baseless for at least the following reasons:

(A) TorPharm will not infringe the '505 and '791 patents because its ANDA product will not include a wetting agent;

(B) TorPharm will not infringe the '505 and '791 patents because its ANDA product will not include a sugar;

(C) TorPharm will not infringe the '505 and '791 patents because its ANDA product will not include a sugar as wetting agent.

65. Upon information and belief, Biovail further knew that the litigation was baseless because it knew, or should have known, that its claim that the patent encompassed all sugars of any kind, first revealed to the Court on February, 2003, rendered the patent invalid for lack of enablement, lack of utility, indefiniteness, overbreadth, inoperability and for invalidity based upon prior art. Biovail knew, or should have known, at the time of filing that its position on the scope of term "sugar" rendered the '791 and the '505 patents invalid and the lawsuit baseless.

66. As a result of the above violations TorPharm has been, or will imminently be, injured in its business and property.

COUNT XIII

67. TorPharm incorporates by reference herein, paragraphs 1-66 of its counterclaims.

68. This Counterclaim is brought for monopolization pursuant to § 2 of the Sherman Act, 15 U.S.C. §2.

69. Jurisdiction is predicated upon 28 U.S.C. §§ 1131 and 1337.

70. Biovail knew, or should know, that the '791 and the '505 patents are invalid and unenforceable due to knowing and willful fraud before the PTO in procuring the patents.

71. Assuming that Biovail's representation that sugar encompassed all sugars, Biovail failed to disclose to the PTO that the claims of the '791 and the '505 patents lacked enablement and utility and were indefinite and overbroad and inoperable. Biovail willfully misrepresented the novelty of the invention which, in fact, was invalid based upon prior art.

72. As a result of the above violations TorPharm has been injured in its business and property.

PRAYER FOR RELIEF

WHEREFORE, TorPharm requests that this Honorable Court:

a. Deny Biovail all requested relief and dismiss the Amended Complaint with prejudice.

b. Adjudge and decree that the '791 and '505 patents are not infringed.

c. Adjudge and decree that the '791 and '505 patents are invalid as anticipated by the prior art under 35 U.S.C. § 102 and/or obvious over the prior art under 35 U.S.C. § 103.

d. Order that the effective date of the approval of TorPharm's Abbreviated New Drug Applications (ANDA) is immediate under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), and its use, upon a statement by the FDA that it is otherwise ready to approve the ANDAs.

e. TorPharm further requests that this Court award it its attorneys' fees, interests and costs.

f. TorPharm requests that it be granted such other and further relief as this Court deems just and proper.

g. Adjudge and decree that the '791 and '505 patents are invalid as indefinite, lacking enablement, overbroad, and/or inoperable under 35 U.S.C. § 112.

h. Adjudge and decree that the '791 and '505 patents are invalid due to overbreadth of the claims thereof under 35 U.S.C. §§ 102, 103, and/or 112.

i. Adjudge and decree that the '791 and '505 patents are invalid as lacking utility and/or being inoperable due to overbreadth under 35 U.S.C. § 101.

j. Award threefold damages and award of attorneys' fees and costs on the antitrust claims set forth in Counts XII and XIII.

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

July _____, 2004

By_____

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EXHIBIT B

US005529791A

United States Patent [19]

Deboeck et al.

[11] Patent Number: 5,529,791

[45] Date of Patent: Jun. 25, 1996

[54] **EXTENDED RELEASE FORM OF DILTIAZEM**

[75] Inventors: **Arthur M. Deboeck**, Gurabo, Puerto Rico; **Philippe R. Baudier**, Waterloo, Belgium

[73] Assignee: **Galephar P.R., Inc., Ltd.**, Carolina, Puerto Rico

[21] Appl. No.: **311,722**

[22] Filed: **Sep. 23, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 68,951, May 28, 1993, abandoned, which is a continuation of Ser. No. 721,396, Jun. 26, 1991, Pat. No. 5,288,505.

[51] **Int. Cl.**[6] **A61K 9/16**; A61K 9/58; A61K 9/62

[52] **U.S. Cl.** **424/494**; 424/490; 424/497; 514/777; 514/785; 514/786; 514/970

[58] **Field of Search** 424/457, 458, 424/462, 490, 493, 497, 498, 499, 494

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,112,621	5/1992	Stevens et al.	424/497
5,275,824	1/1994	Carli et al.	424/490

Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

4 Claims, 2 Drawing Sheets

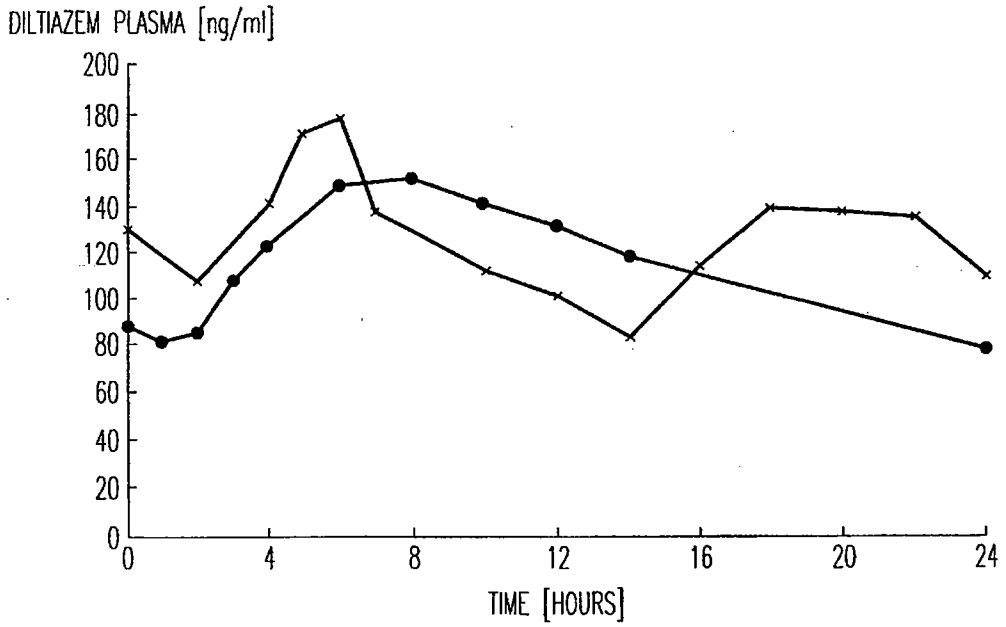
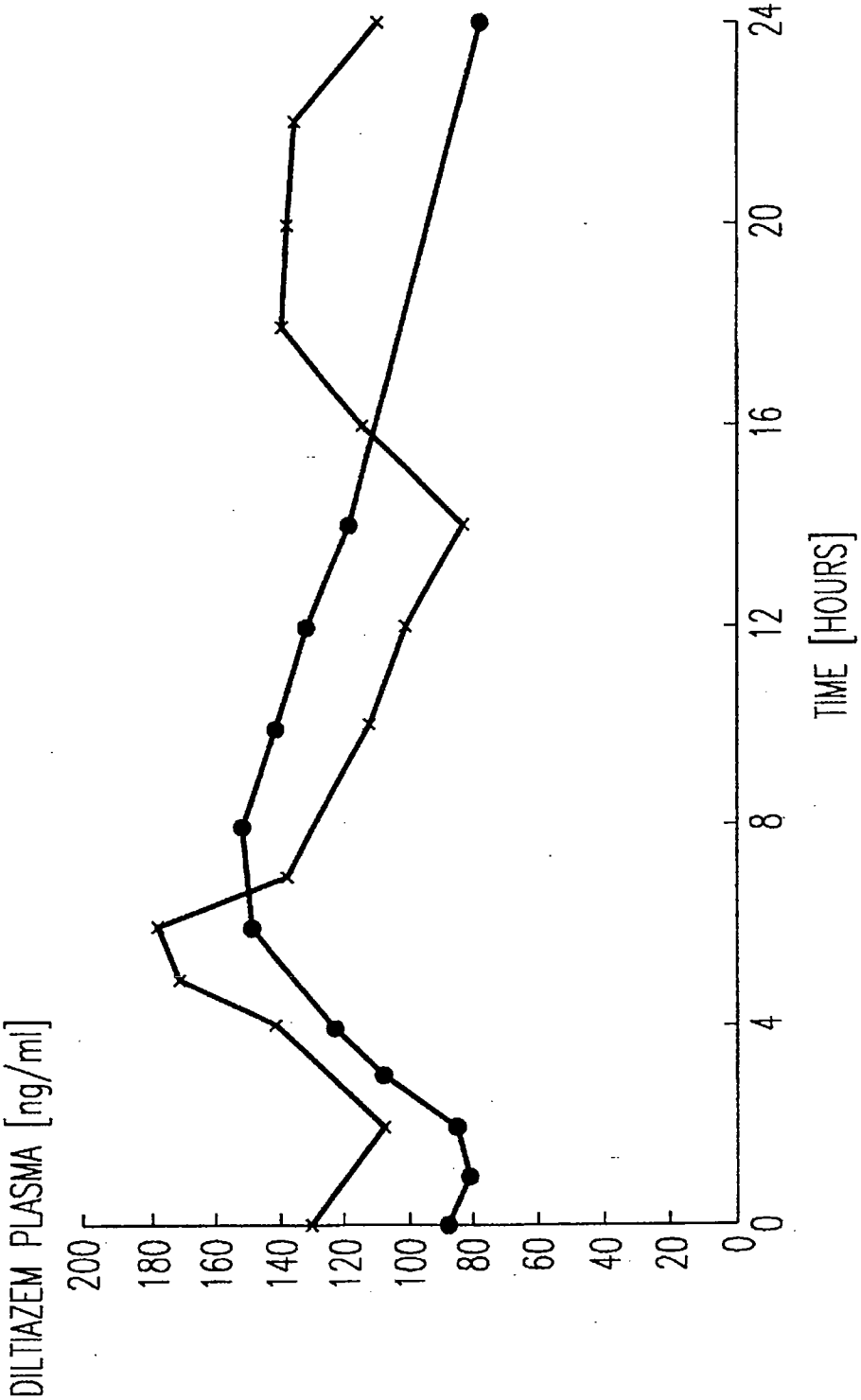


FIG. 1


DILTIAZEM PLASMA [ng/ml]
200
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
TIME [HOURS]

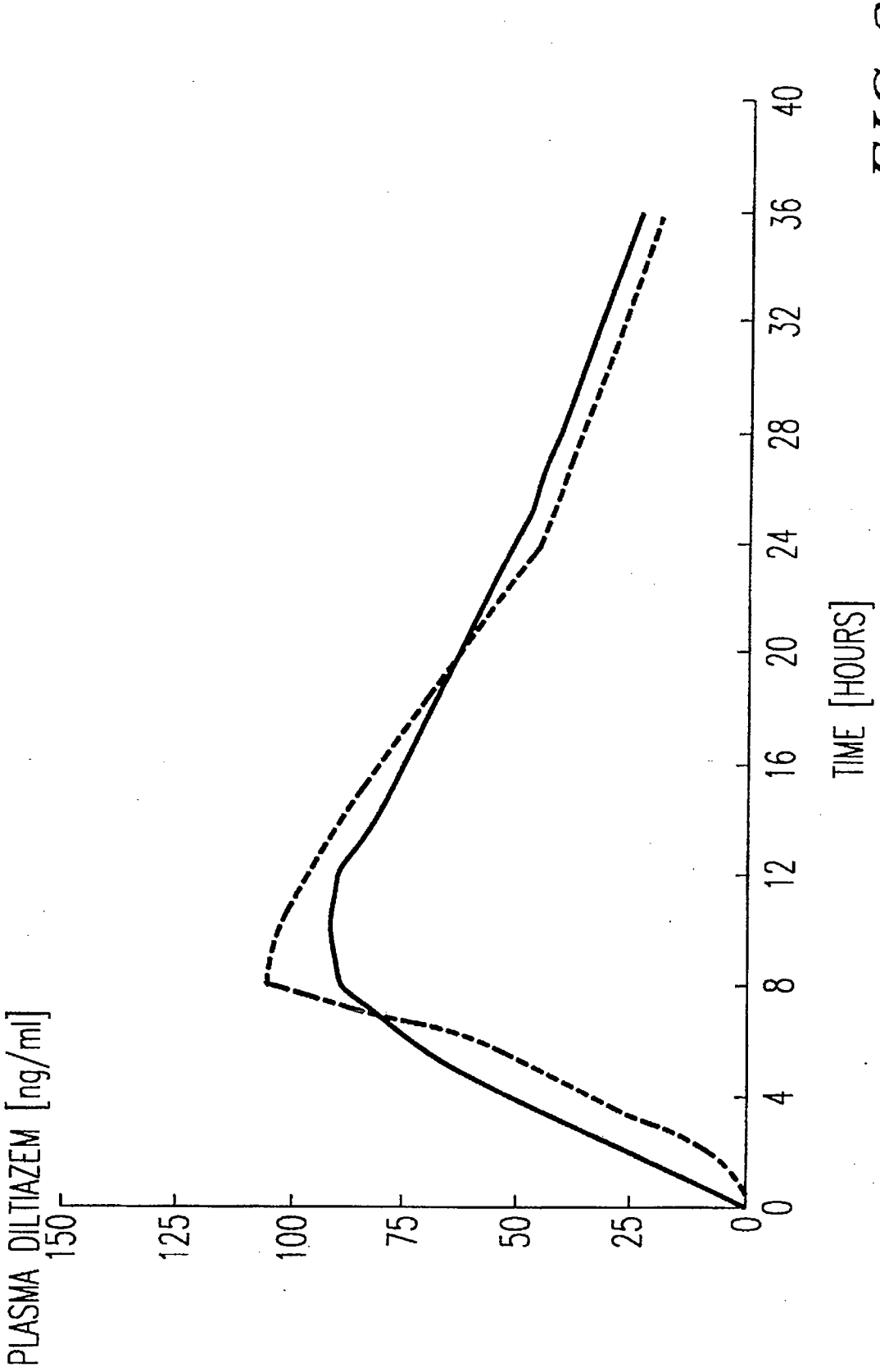

PLASMA DILTIAZEM [ng/ml]
150
125
100
75
50
25
0
0
4
8
12
16
20
24
28
32
36
40
TIME [HOURS]

FIG. 2

EXTENDED RELEASE FORM OF DILTIAZEM

This application is a continuation of application Ser. No. 08/068,951, filed on May 28, 1993, now abandoned, which is a continuation of application Ser. No. 07/721,396 filed Jun. 26, 1991, now U.S. Pat. No. 5,288,505.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

2. Description of the Background

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension; either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in human is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-released of Diltiazem known under the trade name CARDIZEM SR® was developed and presented in the form of "erodible pellets", U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2,(4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they

may also include the acetate, citrate or lactate salts, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane whereof the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

saccharose, mannitol, sorbitol;

lecithins;

polyvinylpyrrolidones;

C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as: Microcrystalline celluloses, such as Avicel products (FMC, U.S.A); methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches.

Among the water-soluble and/or dispersible film forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS-30 D of Röhm Pharma (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropylmethylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;

pigments, such as iron oxides and titanium oxide;

fillers, such as lactose and sucrose;

wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;

lubricants, such as magnesium stearate and talc;

antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membrane may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tractus, said process entailing preparing beads and coating the same with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder of ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the collette (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of anyone of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

20 to 85%; Diltiazem hydrochloride

2 to 20% sucroesters WE 15 (wetting agent);

5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);

2 to 10% Methocel E 5 (hydroxypropylmethylcelulose of DOW, U.S.A.);

1 to 15% polyvinylpyrrolidone and

5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pul-

verization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only example and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of duretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting form an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plastifying agent)
0.01 to 2% silicone oil (antifoaming agent);
0.05 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended release galenic forms, a process for preparing the same, therapeutic applications therefor and pharmacokinetic controls using the present galenic forms.

Example 1—beads manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	140 g
Povidone k 30	21 g

After introducing the powders into a planetary mixer and granulating same though the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

Example 2

Diltiazem Hydrochloride	560 g
Crodesta F 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone k 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. There after 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spagetties". A spheronizer type caleva is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C. the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

Example 3

Beads prepared in Example 1 were coated in a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition:

Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone k 30	5.0 g
Eudragit NE30D	620.0 g
Talc USP	17.5 g
water	338.0 g
Simethicone	1.0 g
Tween 80	0.8 g

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate butter pH 5.8 and the revolution speed 100 rpm.

elapsed time [h]	percent dissolved [%]
1	5
4	34
8	62
12	84

Example 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

Coating suspension:

Magnesium stearate	0.636 kg
Talc	0.636 kg

-continued

Titanium dioxide	0.0909 kg
Hydroxypropylmethylcellulose	0.200 kg
Polysorbate 80 NF	0.007 kg
Simethicone c emulsion	0.018 kg
Eudragit NE 30 D	12.4 kg
purified water	6.7 kg

Dissolution "in vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained of 37±0.5° C.

elapsed time [h]	percent dissolved [%]
2	9
4	33
6	54
8	82

Pharmacokinetical results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Pat. No. 4,721,619. (Cardizen SR®) therefore 6 healthy subject received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) during 7 days. At each of the eight day, 11 samples of blood were withdrawn when product of Example 4 was administered and 15 blood samples where withdrawn after the Cardizen SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. FIG. 1 shows the results obtained: the continuous line represent the Diltiazem plasma levels obtained with the product of Example 4 and the broken line the Diltiazem plasma levels of Cardizen SR®.

FIG. 1

Pharmacokinetical parameters:

	Units	Example 4	Cardizen SR ®
Area under the curve [0–24 h]	mg.h/ml	2782 ± 1037	2864 ± 1222
Maximal concentration	mg/ml	116.3 ± 54.1	192.7 ± 85.3
Time of maximum concentration	h	8.0 ± 1.8	5.2 ± 2.8
Fluctuation	%	85.7 ± 25.7	109.5 ± 25
Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3	6.7 ± 3.7

From these results the following conclusion can be drawn:

First, FIG. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Second, the bioavailability, expressed by the areas under the curve of the 2 products, is equivalent (no statistical detectable difference).

Third, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR® after a twice daily administration.

Fourth, the time during the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with product of the previous art when given twice daily.

Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross over study. Blood samples were obtained before and until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment at an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. FIG. 2 curves shows the mean plasma levels obtained when the product is taken without food and the dotted curve the mean plasma levels obtained when the product is taken with food.

FIG. 2

Pharmacokinetics parameter - product of Example 4

	Units	Fasting	Food
Area under the curve (total	mg. h/ml	1988 ± 119	1925 ± 109
Mean residence time	h	21.3 ± 0.7	19.9 ± 0.9
K_a	h^{-1}	0.283 ± 0.024	0.300 ± 0.027
Maximum concentration	mg/ml	100 ± 4.8	112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20% regarding area under the curve, mean residence time and maximum concentration. The larger interval obtained for K_a was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.%).

From all the results it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the one obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract

or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant,

and wherein the wetting agent is selected from the group consisting of sugars, C_{12}-C_{20} fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

2. The composition of claim **1**, wherein the wetting agent is a sugar.

3. The composition of claim **1**, wherein the effective amount of the wetting agent is about 8% by weight of the composition.

4. The composition of claim **1**, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropylmethyl-cellulose and the water, acid- and base- insoluble polymer is an acrylic polymer.

* * * * *

EXHIBIT C

US005288505A

United States Patent [19]

Deboeck et al.

[11] Patent Number: 5,288,505

[45] Date of Patent: Feb. 22, 1994

[54] **EXTENDED RELEASE FORM OF DILTIAZEM**

[75] Inventors: **Arthur M. Deboeck, Gurabo, P.R.; Philippe R. Baudier, Waterloo, Belgium**

[73] Assignee: **Galephar P.R., Inc., Ltd., Carolina, P.R.**

[21] Appl. No.: **721,396**

[22] Filed: **Jun. 26, 1991**

[51] Int. Cl.[5] **A61K 9/16; A61K 9/58**

[52] U.S. Cl. **424/497**; 424/457; 424/458; 424/462; 424/490; 424/499; 424/502

[58] Field of Search 424/499, 457, 458, 462, 424/490, 493, 498, 497

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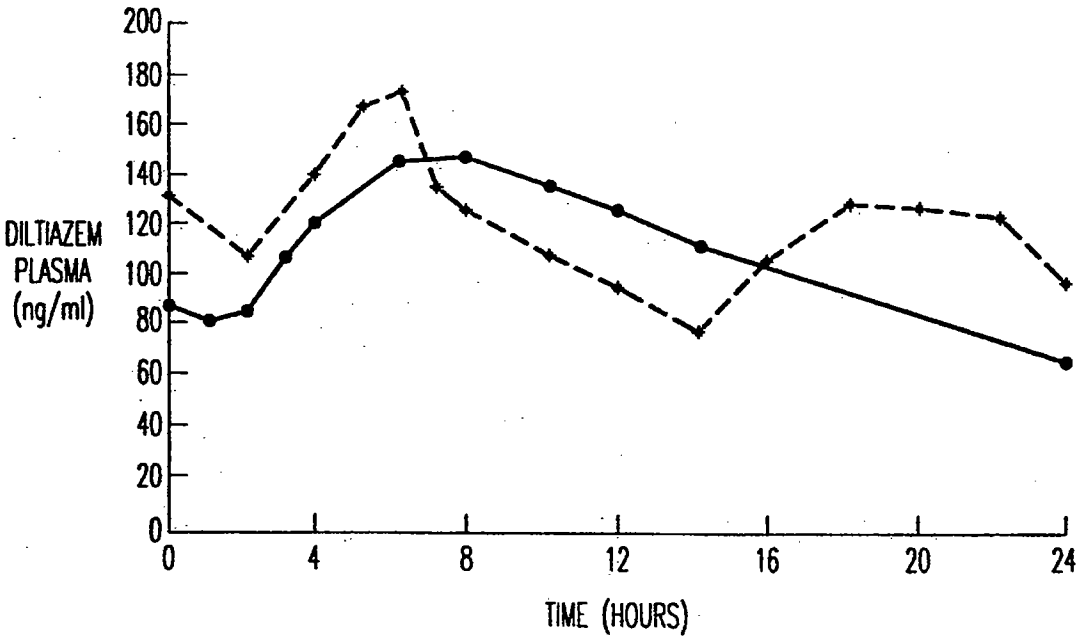
Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

15 Claims, 2 Drawing Sheets



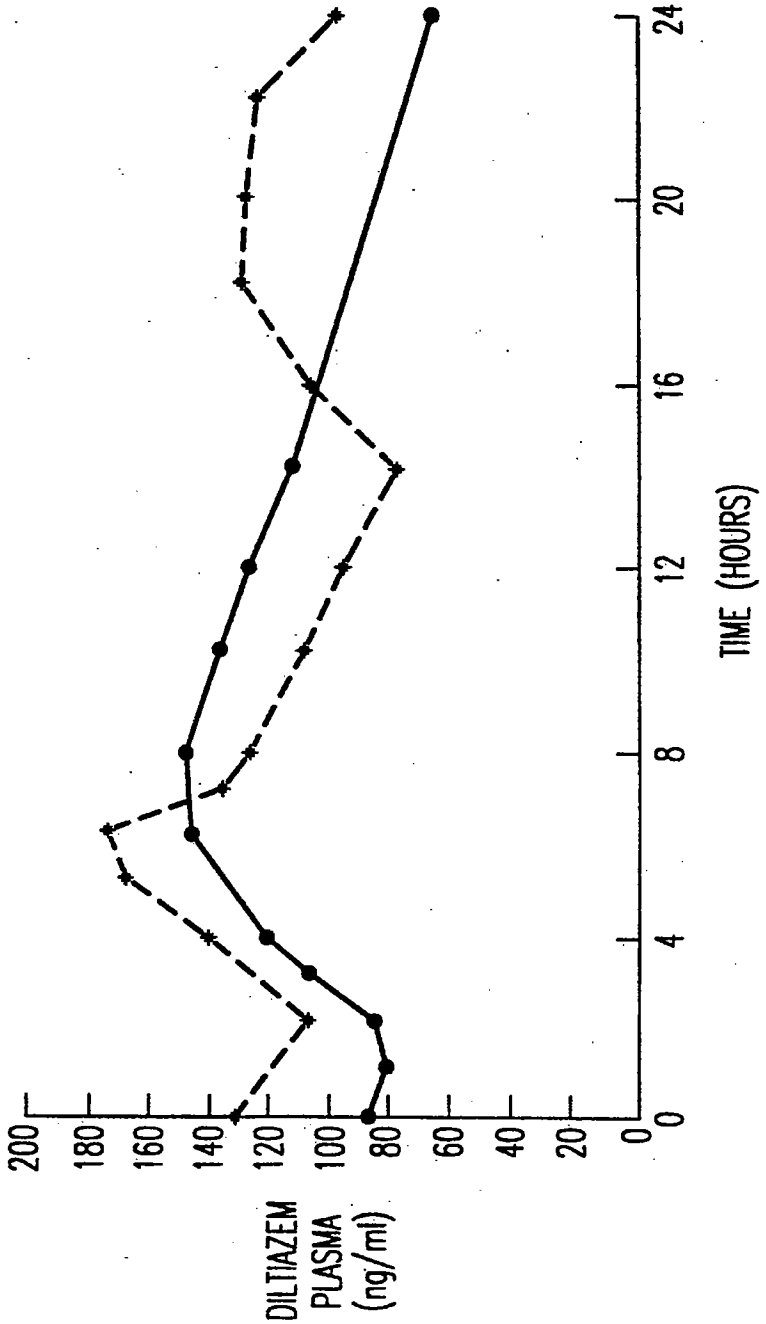

DILTIAZEM PLASMA (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
TIME (HOURS)

FIG. 1

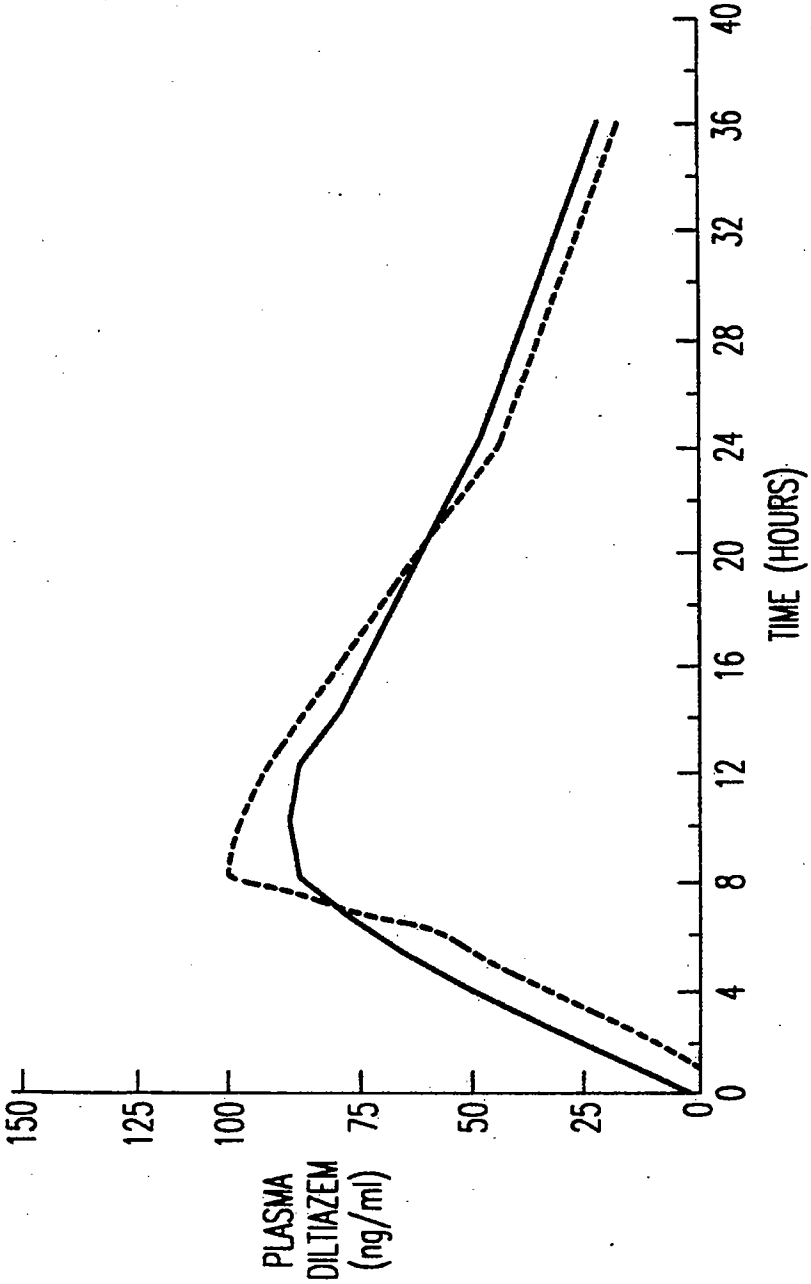

PLASMA DILTIAZEM (ng/ml)
150
125
100
75
50
25
0
0
4
8
12
16
20
24
28
32
36
40
TIME (HOURS)

FIG. 2

EXTENDED RELEASE FORM OF DILTIAZEM

BACKGROUND OF THE INVENTION

1. Field of the Invention

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Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in human is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-released of Diltiazem known under the trade name CARDIZEM SR ® was developed and presented in the form of "erodible pellets", U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2,(4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they may also include the acetate, ci-

trate or lactate salts, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane whereof the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

- sugars, for example saccharose, mannitol, sorbitol and lactose;
- lecithins;
- C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);
- xylose esters or xylites;
- polyoxyethylenic glycerides;
- esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);
- sorbitan fatty acid esters (Span, Atlas, U.S.A.);
- polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as: Microcrystalline celluloses, such as Avicel products (FMC, U.S.A); methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches.

Among the water-soluble and/or dispersible film forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS - 30 D of Röhm Pharma (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropylmethylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

- plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;
- pigments, such as iron oxides and titanium oxide;
- fillers, such as lactose and sucrose;
- wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;
- lubricants, such as magnesium stearate and talc;
- antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membrane may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tract, said process entailing preparing beads and coating the salt with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder of ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the collette (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of anyone of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

- 20 to 85%; Diltiazem hydrochloride
- 2 to 20% sucroesters WE 15 (wetting agent);
- 5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);
- 2 to 10% Methocel E 5 (hydroxypropylmethylcelulose of DOW, U.S.A.);
- 1 to 15% polyvinylpyrrolidone and
- 5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or disper-

sion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pulverization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only example and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting from an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plastifying agent)
0.01 to 2% silicone oil (antifoaming agent);
0.05 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended release galenic forms, a process for preparing the same, therapeutic applications therefor and pharmacokinetic controls using the present galenic forms.

EXAMPLE 1

Beads Manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	140 g
Povidone k 30	21 g

After introducing the powders into a planetary mixer and granulating same though the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

EXAMPLE 2

Diltiazem Hydrochloride	560 g
Crodesta F 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone k 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. There after 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spagetties". A spheronizer type caleva is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

EXAMPLE 3

Beads prepared in Example 1 were a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition:	
Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone k 30	5.0 g
Eudragit NE30D	620.0 g
Talc USP	17.5 g
water	338.0 g
Simethicone	1.0 g
Tween 80	0.8 g

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate butter pH 5.8 and the revolution speed 100 rpm.

elapsed time [h]	percent dissolved [%]
1	5
4	34
8	62
12	84

EXAMPLE 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

Coating suspension:	
Magnesium stearate	0.636 kg
Talc	0.636 kg
Titanium dioxide	0.0909 kg
Hydroxypropylmethylcellulose	0.200 kg
Polysorbate 80 NF	0.007 kg
Simethicone c emulsion	0.018 kg
Eudragit NE 30 D	12.4 kg
purified water	6.7 kg

Dissolution "In Vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained of 37°±0.5° C.

elapsed time [h]	percent dissolved [%]
2	9
4	33
6	54
8	82

Pharmacokinetical Results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Pat. No. 4,721,619. (Cardizen SR ®) therefore 6 healthy subject received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) during 7 days. At each of the eight day, 1 samples of blood were withdrawn when product of Example 4 was administered and 15 blood samples where withdrawn after the Cardizen SR ® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. FIG. 1 shows the results obtained: the continuous line represent the Diltiazem plasma levels obtained with the product of Example 4 and the broken line the Diltiazem plasma levels of Cardizen SR ®.

FIG. 1

Pharmacokinetical parameters:	Units	Example 4	Cardizen SR ®
Area under the curve [0-24 h]	mg.h/ml	2782 ± 1037	2864 ± 1222
Maximal concentration	mg/ml	116.3 ± 54.1	192.7 ± 85.3
Time of maximum concentration	h	8.0 ± 1.8	5.2 ± 2.8
Fluctuation	%	85.7 ± 25.7	109.5 ± 25
Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3	6.7 ± 3.7

From these results the following conclusion can be drawn:

First, FIG. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Second, the bioavailability, expressed by the areas under the curve of the 2 products, is equivalent (no statistical detectable difference).

Third, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR ® after a twice daily administration.

Fourth, the time during the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with product of the previous art when given twice daily.

Food Effect Study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross over study. Blood samples were obtained before and until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment at an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. FIG. 2 curves shows the mean plasma levels obtained when the product is taken without food and the dotted curve the mean plasma levels obtained when the product is taken with food.

FIG. 2

Pharmacokinetics parameter - product of Example 4	Units	Fasting	Food
Area under the curve (total	mg.h/ml	1988 ± 119	1925 ± 109
Mean residence time	h	21.3 ± 0.7	19.9 ± 0.9
K_a	h^{-1}	0.283 ± 0.024	0.300 ± 0.027
Maximum concentration	mg/ml	100 ± 4.8	112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20% regarding area under the curve, mean residence time and maximum concentration. The larger interval obtained for K_a was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.%).

From all the results it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the one obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable

salts thereof, which comprises beads, said beads consisting essentially of in admixture together:

a) an effective amount of Diltiazem or said one or more salts thereof as an active ingredient, and

b) an effective amount of a wetting agent, wherein said wetting agent is selected from the group consisting of a sugar, a C_{12}–C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically-acceptable adjuvant.

2. The extended-release galenical composition of claim 1, wherein said salt is the hydrochloride salt.

3. The extended-release galenical composition of claim 1, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

4. The extended-release galenical composition of claim 3, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

5. The extended-release galenical composition of claim 1, wherein the weight of the Diltiazem salt is about 20 to 95% by weight.

6. A pharmaceutical composition, comprising an extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable salts thereof, which comprises in capsule form:

a) beads consisting essentially of an effective amount of each of Diltiazem or said one or more salts thereof and a wetting agent in admixture together, wherein said wetting agent is selected from the group consisting of a sugar, a C_{12}–C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide ester, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

b) one or more other pharmaceutically active ingredients which are pharmaceutically compatible with Diltiazem or said one or more salts thereof.

7. The pharmaceutical composition of claim 6, wherein said one or more other pharmaceutically active ingredients comprise-β-adrenoceptor or diuretic compounds or compositions containing the same.

8. The pharmaceutical composition of claim 6, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

9. The pharmaceutical composition of claim 6, wherein said salt is the hydrochloride salt.

10. The pharmaceutical composition of claim 6, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

11. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition consisting essentially of Diltiazem or one or more pharmaceutically-acceptable salts thereof and a wetting agent in admixture together in the form of beads, wherein the wetting agent is selected from the group consisting of a sugar, a C_{12}–C-fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, an alcohol-polyglycide ester, a glyceride-polyglyceride lecithins and a combination thereof, and

wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable excipient.

12. The method of claim 11, wherein said administration is orally and once per day.

13. The method of claim 11, wherein said mammal is a human.

14. The method of claim 12, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts are administered in total per day.

15. The method of claim 11, wherein said salt is the hydrochloride salt.

* * * * *

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

BIOVAIL LABORATORIES, INC., a corporation of Barbados,	)	
Plaintiff,	)	No.: 02-7119
vs.	)	
	)	Judge: Anita B. Brody
TORPHARM, INC., a Canadian Corporation,	)	
Defendant.	)	

BIOVAIL LABORATORIES, INC.'S
MEMORANDUM OF LAW ON CLAIM CONSTRUCTION

I. PRELIMINARY STATEMENT

TorPharm's claim construction is incorrect for two reasons. First, TorPharm ignores the well-settled principle that a dictionary definition cannot trump a term that is defined by the very language of the claim. Thus, a "wetting agent" is clearly defined in the claim of each patent by the "wherein" clause:

> wherein said wetting agent is selected from the group consisting of a sugar, a C.sub.12 -C.sub.20 fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof

E.g., U.S. Patent No. 5,288,505 ("the '505 patent") (Exhibit 1), Claim 1, Col. 9, lines 5-13. See also, U.S. Patent No. 5,529,791 ("the '791 patent") (Exhibit 2), Claim 1, Col. 9, lines 7-13.

TorPharm's collateral estoppel argument is entirely misplaced. In patent law cases, the law of the regional circuit applies to the issue of collateral estoppel (also called

"issue preclusion"). *Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1345 (Fed. Cir. 2002). In the Third Circuit, "unless resolution of claims was essential to affirmance on appeal, issue preclusion will not bar re-litigation of those issues." *Arab African Int'l Bank v. Epstein,* 958 F.2d 532 (3d Cir. 1992), *rev'd on other grounds*, 10 F.3d 168 (3d Cir. 1993). The Federal Circuit has applied the same principle to its decisions. *Masco Corp. v. United States*, 303 F.3d 1316, 1329 (Fed. Cir. 2002).

As will be explained below, the Federal Circuit in *Biovail v. Andrx*, 239 F.3d 1297, 1301 (Fed. Cir. 2001) explicitly reserved ruling on the claim construction issue:

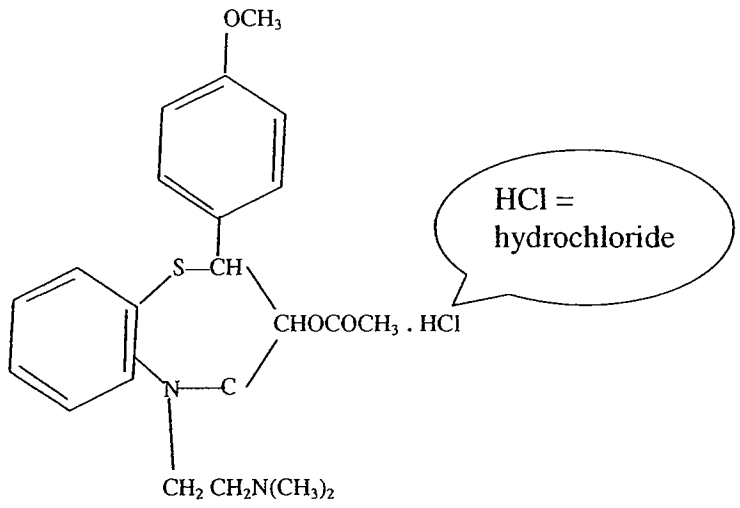
> It is not necessary for this court to construe the term "wetting agent." That is, the outcome of this case does not hinge on whether the sugar used in the core of Andrx's product meets the "wetting agent" limitation of claim 1 of the *'791* patent.

Thus, under both Third Circuit and Federal Circuit law, Biovail is not bound by the lower court's interpretation of the term "wetting agent" in that case.

TorPharm argues in its claim interpretation brief that methylcellulose is not a sugar. As this Court noted at the hearing on May 8, whether methylcellulose is a "sugar" (one of the compounds specifically defined by the claim as a "wetting agent") is an infringement issue, not a claim interpretation issue. Indeed, this infringement issue is the subject of the conflicting expert reports that have been filed by the parties with respect to TorPharm's motion for summary judgment.

II. BRIEF TUTORIAL

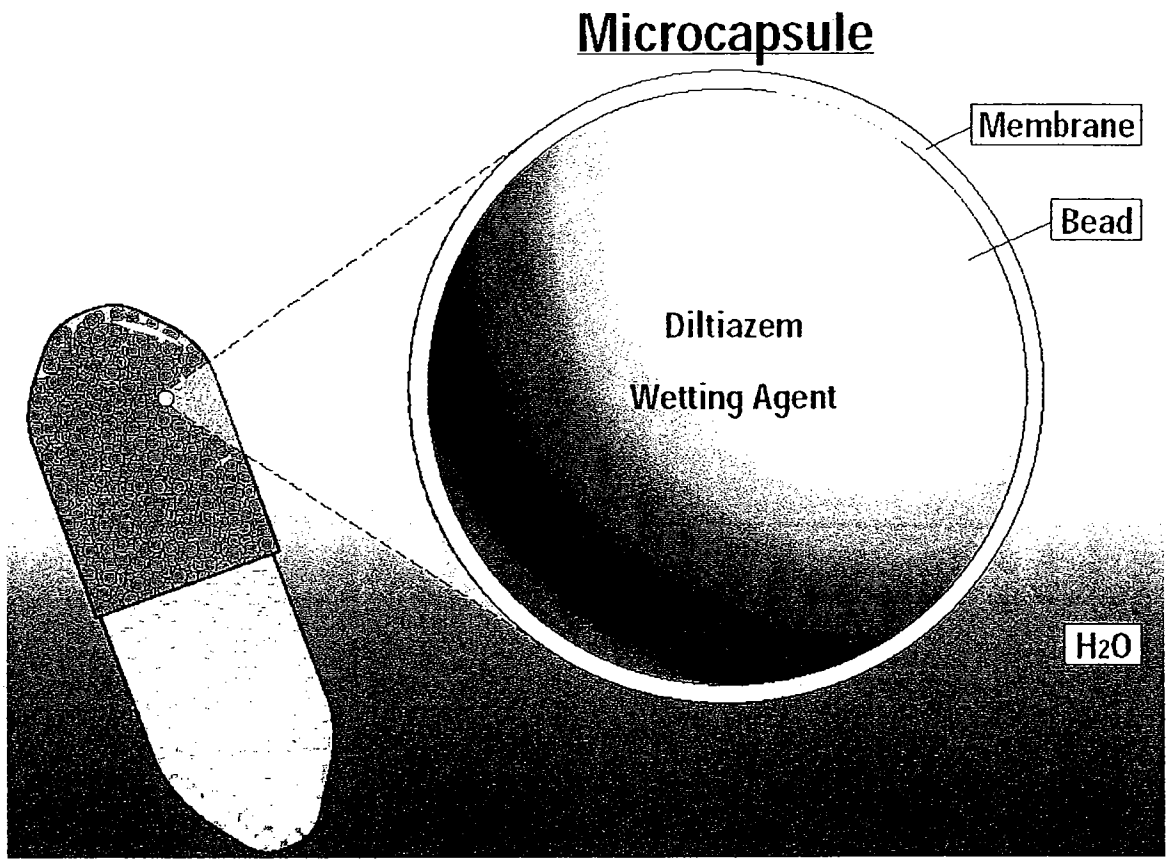
Diltiazem is a drug that is used to treat angina and hypertension. It is classified as a calcium channel blocker. '791 patent, col. 1, lines 16-20. A salt of diltiazem – such as diltiazem hydrochloride – is used in the formulation of the inventions claimed in the '791 and '505 patents. The formula for diltiazem hydrochloride is shown below.



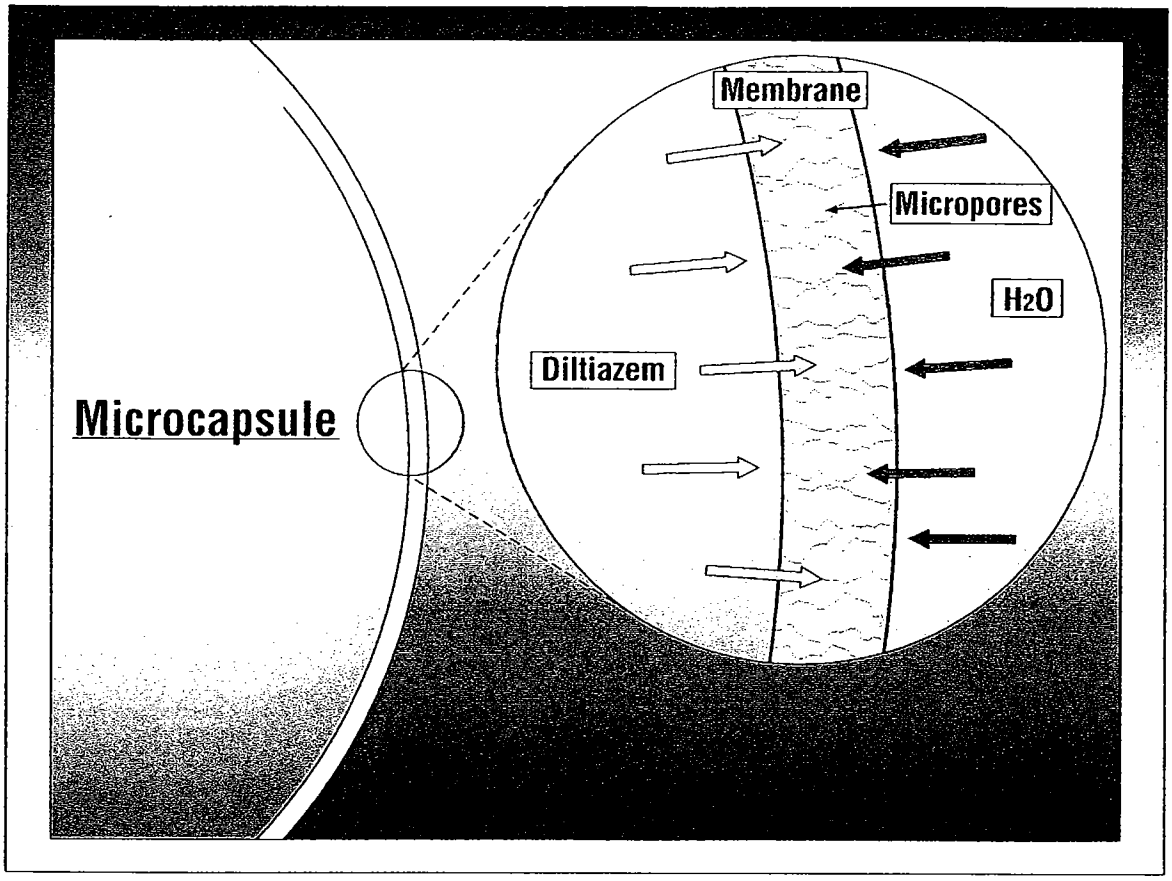
Diltiazem Hydrochloride

Both the '505 and '791 patents are directed to an extended release formulation of diltiazem that may be administered once a day. E.g., '791 Patent, Col. 2, lines 50-53. The formulation of the inventions of the '791 and '505 patents consists of **beads** that contain a diltiazem salt, such as diltiazem hydrochloride, admixed with a wetting agent. '505 Patent, Col. 4, lines 25-53; 791 Patent, Col. 4, lines 25-52.

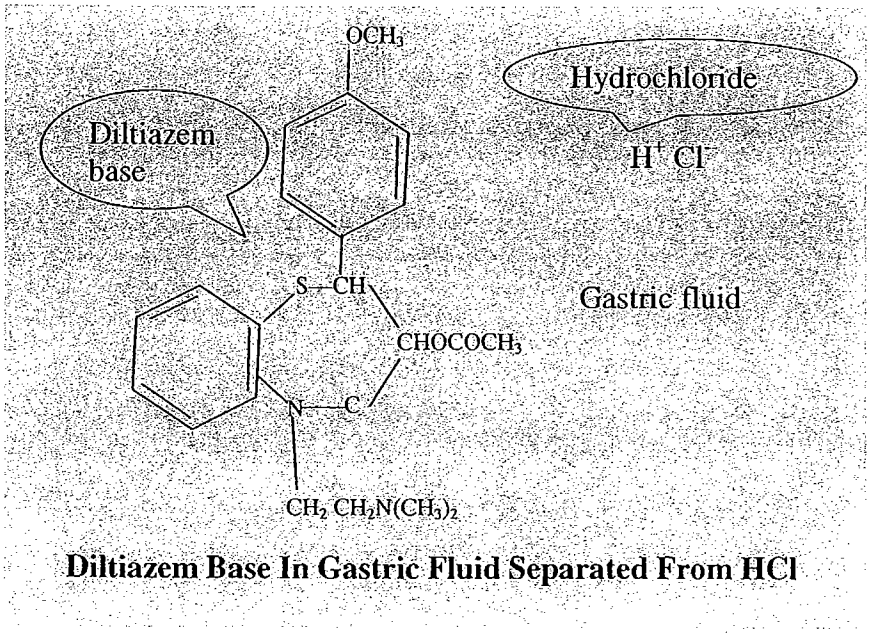
The **beads** are covered with a **microporous membrane**. '505 Patent, Col. 2, lines 54-61; 791 Patent, Col. 2, lines 53-60. For convenience, the membrane-coated beads are referred to as "microcapsules." Enough coated beads to deliver the desired amount of diltiazem are placed in a gelatin capsule, as is shown below.



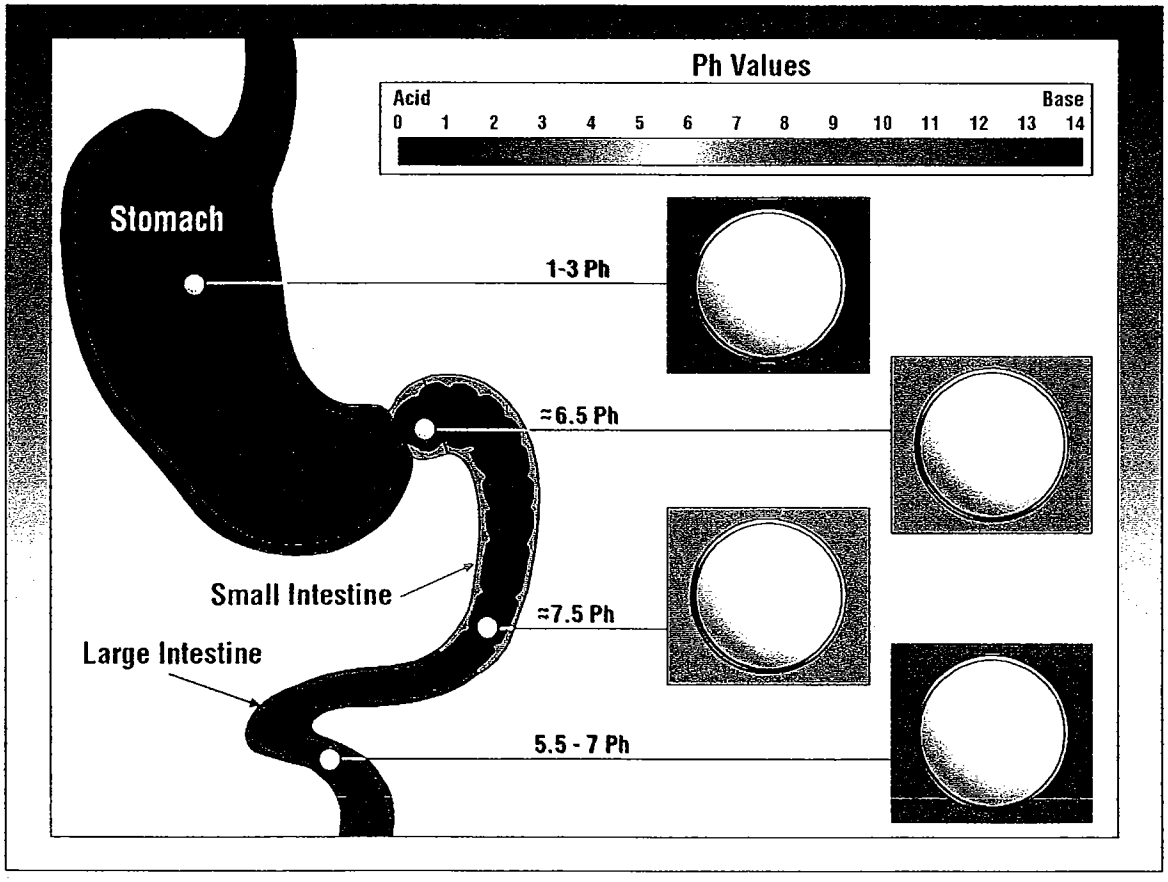
The capsule dissolves in the stomach within several minutes after being ingested. The membrane swells, creating micropores. Gastric fluid penetrates the membrane through the micropores, causing at least some of the diltiazem hydrochloride to dissolve within the membrane, as is shown below.



When diltiazem hydrochloride dissolves, the diltiazem base dissociates from the hydrochloride, as is shown below.



A common measure of whether a liquid is acidic or basic is pH, a logarithmic scale of effective hydrogen ion concentration that varies theoretically from 0 (most acidic) to 7 (neutral) to 14 (most basic). Each portion of the gastrointestinal tract has a different pH. The pH of the stomach ranges from about 1 to about 3. The pH in the small intestine ranges from about 2 to about 7.8. The pH of the large intestine ranges from about 5.5 to about 7. The pH of the gastrointestinal tract varies when food is eaten. See Exhibit 3, attached hereto, as well as the illustration below.



As the microcapsules travel through the gastrointestinal tract (from the stomach to the small intestine and then the large intestine), diltiazem is continuously released through the micropores of the membrane. Diltiazem remains soluble – in other words, in solution within the membrane as the membrane-coated bead moves through the

gastrointestinal tract and is subjected to different pH. The membrane stays intact throughout the entire length of the gastrointestinal tract. Diltiazem continues to be released through the membrane as the coated bead passes through the gastrointestinal tract.

The patent explains that the formulation is free from a "food effect." "The product . . . given with food is bioequivalent to the administration without food." '791 Patent, Col. 8, lines 40-42. Thus, the release of diltiazem from the microcapsules of the invention is not materially affected by differences in pH as the microcapsules pass through the GI tract.

III. BIOVAIL'S PROPOSED INTERPRETATION OF THE CLAIMS

At the May 8, 2003 hearing, this Court requested that the each party provide the Court with a claim chart, specifically setting forth the party's proposed construction of the terms at issue in this case. Biovail's claim chart is set forth below.

Claim 1 of '505 Patent	**Biovail's Proposed Interpretation**
[preamble] An extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable salts thereof, which comprises beads, said beads consisting essentially of in admixture together:	Not at issue.
[i] a) an effective amount of Diltiazem or said one or more salts thereof as an active ingredient, and	Not at issue.
[ii] b) an effective amount of a **wetting agent,**	The term "wetting agent" is defined by the Markush group set forth in part **[iii]** below

Claim 1 of '505 Patent	Biovail's Proposed Interpretation
[iii] wherein **said wetting agent is selected from the group consisting of** a sugar, a C.sub.12 -C.sub.20 fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,	This portion of the claim is a Markush group and defines the term "wetting agent" in part **[ii]**
[iv] wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically-acceptable adjuvant.	Not at issue.

Claim 1 of the '791 Patent	Biovail's Proposed Interpretation
1. **[preamble]** An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises	Not at issue
[i] beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient,	Not at issue
[ii] each bead containing one or more of the Diltiazem salts and	Not at issue
[iii] an effective amount of a **wetting agent** in admixture with the one or more Diltiazem salts	The term "wetting agent" is defined by the Markush group set forth in part **[vi]** below
[iv] to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein,	Diltiazem is in solution within the membrane of the coated bead so that it can be released through the membrane as the membrane-coated bead travels through the entire length of the gastrointestinal tract, and the release of diltiazem is unaffected within the tolerances disclosed in the patent by the presence or absence of food.

Claim 1 of the '791 Patent	Biovail's Proposed Interpretation
[v] said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant, and	Not at issue.
[vi] wherein **the wetting agent is selected from the group consisting of** sugars, C12-C20 fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.	This portion of the claim is a Markush group and defines the term "wetting agent" in part **[iii]**

IV. THE TERM "WETTING AGENT" INCLUDES SUGARS

A. It Is Improper To Rely On Dictionary Definitions That Contradict Explicit Claim Language

The Federal Circuit has recently cautioned that the interpretation of a claim begins with the claim language itself. "As usual, the most important indicator of the meaning of [the word in dispute] is its usage and context within the claim itself." *Middleton, Inc. v. 3M*, 311 F.3d 1384, 1387 (Fed. Cir. 2002). Moreover, "[i]n construing claims, the analytical focus must begin and remain centered on the language of the claims themselves, for it is that language that the patentee chose to use to 'particularly point[ ] out and distinctly claim[ ] the subject matter which the patentee regards as his invention.' *35 U.S.C. § 112*, P 2." *Texas Digital Systems, Inc. v. Telegenix, Inc.*, 308 F.3d 1198, 1201-02 (Fed. Cir. 2002).

Texas Digital is cited by TorPharm for the proposition that the Court may consult dictionaries to define terms in claims. *Texas Digital*, however, does not stand for the blanket proposition that dictionary definitions must always be used to define claim terms. On the contrary, the Court firmly pointed out that dictionary definitions that are contrary to the specification and claim language must be rejected:

> [T]he intrinsic record may show that the specification uses the words in a manner clearly inconsistent with the ordinary meaning reflected, for example, in a dictionary definition. In such a case, the inconsistent dictionary definition must be rejected. See id. ("[A] common meaning, such as one expressed in a relevant dictionary, that flies in the face of the patent disclosure is undeserving of fealty.")

Id., at 1204.

In this case, the claim language explicitly contradicts TorPharm's proposed dictionary definitions of the term "wetting agent." Each claim defines "wetting agent" in terms of a "Markush group." A "Markush group" is an "acceptable form of alternative expression" sanctioned by the USPTO and based on the decision *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). *See Manual Of Patent Examining Procedure*, §2173.05(h). Exhibit 4. A Markush group is expressed in the form "selected from the group consisting of A, B and C." Id. In order to list several compounds as a Markush group, "it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship." Id. Markush claim define alternative ingredients. " *See* LANDIS, MECHANICS OF PATENT CLAIMS DRAFTING § 50 (Robert C. Faber, ed., 1997). Thus, Markush groups by their terms provide definitions, and this case is no different.

In the patents in suit, the patent specification discloses that the compounds listed act as wetting agents when combined with diltiazem or one of its salts in the membrane-coated bead.

The '505 patent defines wetting agent as follows:

> **[iii]** wherein said wetting agent is **selected from the group consisting of a sugar**, a C.sub.12 -C.sub.20 fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

The '791 patent includes a similar definition:

> **[vi]** wherein the wetting agent is **selected from the group consisting** of **sugars**, C12-C20 fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

Thus, in both claims, "wetting agents" are those classes of compounds that are listed in the Markush groups. **Sugars** are specifically included.

TorPharm cites various dictionaries that define "wetting agent" as "surface active" agents or surfactants. *See TorPharm's Brief Regarding Claim Construction, Exhibit E.* While these may be normal and conventional definitions of "wetting agents," that is not how the term is used in the claims of either patent in suit.

TorPharm's expert, Dr. Goldberg, has argued in paragraph 43 of his supplemental expert report that "Sucrose . . . is not a surface-active agent." Thus, according to Dr. Goldberg, TorPharm's dictionary definitions are inappropriate in this case, because they

would exclude sugar – a term that is specifically **included** in the Markush groups – from the definition of wetting agent.

The very specific definition of "wetting agent" in the Markush groups of the claims of the '505 and '791 patent unambiguously define the term. No further definition is needed. *See Biovail Corp. v. Andrx Pharmaceuticals, Inc.*, 239 F.3d 1297, 1301 n.1 (Fed. Cir. 2001) ("If intrinsic evidence, including the Markush group in claim 1 and the list of wetting agents in the specification of the *'791* patent unambiguously define the term "wetting agent," then the district court's reliance on expert testimony to construe this term was improper.").

B. The Lower Court's Interpretation Of "Wetting Agent" In *Biovail Corp. v. Andrx Pharmaceuticals* Does Not Collaterally Estop Biovail Because The Federal Circuit Did Not Rely On It

TorPharm's collateral estoppel argument is misplaced. It ignores well-settled Third Circuit and Federal Circuit precedent that collateral estoppel or issue preclusion cannot apply to an issue that was not decided on appeal.

1. "Once an appellate court has affirmed on one ground and passed over another, preclusion does not attach to the ground omitted from its decision."

On collateral estoppel or issue preclusion issues, the Federal Circuit applies the law of the regional circuit. *Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1345 (Fed. Cir. 2002). In this Circuit, a lower court decision will not act as collateral estoppel "unless resolution of claims was essential to affirmance on appeal." *Arab Aftrican Int'l Bank v. Epstein*, 958 F.2d 532 (3d Cir. 1992), *rev'd on other grounds*, 10 F.3d 168 (3d Cir. 1993).

The Federal Circuit has explicitly held that "judicial statements regarding the scope of patent claims are entitled to collateral estoppel effect in a subsequent infringement suit only to the extent that determination of scope was essential to a final

judgment on the question of validity or infringement." *In re Freeman*, 30 F.3d 1459, 1466 (Fed. Cir. 1994), *citing A.B. Dick Co.*, 713 F.2d 700, 704 (Fed. Cir. 1983). The Court has "warned, however, that statements regarding the scope of patent claims made in a former adjudication should be narrowly construed." Id. Further, to apply issue preclusion to a claim interpretation issue decided in a prior infringement adjudication, "the interpretation of the claim had to be the reason for the loss [in the prior case] on the issue of infringement." *Jackson Jordan, Inc v. Plasser American Corp.*, 747 F.2d 1567, 1577, (Fed. Cir. 1984).

The Federal Circuit has also made it clear that when a trial court decision is appealed, issue preclusion does not apply to an issue decided by the trial court unless the same issue was essential to the Federal Circuit's decision on appeal. *Masco Corp. v. United States*, 303 F.3d 1316, 1329 (Fed. Cir. 2002). In *Masco*, the government argued that issue preclusion applied to the factual issues of whether a lever was pushed or pulled in the accused device, as a lower court had held in a previous case. Id. The Federal Circuit pointed out that the lower court in the previous case had "also based its decision on other claim limitations" and that the "push/pull" issue was not relied on by the Federal Circuit in affirming the lower court's decision. Id. The Federal Circuit refused apply collateral estoppel or issue preclusion, citing 18 Charles Alan Wright, Arthur R. Miller & Edward H. Cooper, Federal Practice and Procedure § 4421 (2d ed. 2002) ("Once an appellate court has affirmed on one ground and passed over another, preclusion does not attach to the ground omitted from its decision."). Id., at 1330. The Federal Circuit concluded,

> Since we did not reach the push/pull issue in Mas-Hamilton II [the appellate decision], we are constrained by our

> precedent to hold that Masco is not precluded from relitigating the issues of whether the lever is pushed into the cam in the X-07 lock and whether pushing and pulling are equivalent.

Id., at 1331.

2. Contrary To TorPharm's Argument, Biovail Appealed The Trial Court's Interpretation Of Wetting Agent

At the May 8, 2003 status conference, TorPharm's attorneys argued that Biovail had not appealed the trial court's interpretation of "wetting agent" in the *Andrx* case. Nothing could be further from the truth.

In its appeal brief (relevant pages of which are attached as Exhibit 5 hereto), Biovail listed as one of the issues on appeal "[w]hether the trial court erred . . . by rejecting the patentee's definition of the term 'wetting agent' set forth in a Markush group in the claim itself." *Brief of Plaintiff-Appellants*, at p. 2. At page 21 of the same brief, Biovail explained that "[a] Markush group defines a set of alternatives, which the patentee here called "wetting agents." *See* LANDIS, MECHANICS OF PATENT CLAIMS DRAFTING § 50 (Robert C. Faber, ed., 1997) ('Markush claims ***define*** alternative chemical ingredients that can be used in a compound, composition, alternative steps in a process, or alternative choices for an article.')"

On the next page, Biovail pointed out that the prosecution history supported the inclusion of sugars as a wetting agent:

> Thus, the examiner wrote:
>
> > The composition requires a particular type of wetting agent to be effective. Since it is evident that the release profile of the drug is determined by the particular wetting agents in admixture, the limitations of claim 28 are considered critical and should be incorporated into claim 27 for proper enablement

> A3385. Thus, even if the term "wetting agent" has an ordinary meaning to those of skill in the art, the intrinsic evidence of the claims, written description, and prosecution history clearly provide a different, special definition.
>
> The trial court erred by permitting Andrx to contradict this intrinsic definition with the testimony of Dr. Wiener, Andrx's supposed expert in surface chemistry. He testified and the trial court found that sugar is not a wetting agent when it is wet, i.e., the only time it would be available "to maintain the solubility of Diltiazem in each bead" as required by claim element [d]. A3186–87.

Thus, contrary to TorPharm's argument, Biovail appealed the lower court's definition of "wetting agent"

3. The Federal Circuit Did Not Decide The Meaning Of "Wetting Agent" Because "the outcome of this case does not turn on that issue."

There can be no doubt that the Federal Circuit did not decide the "wetting agent" issue in *Biovail Corp. v. Andrx Pharmaceuticals*, *supra*. Indeed, the Federal Circuit made it absolutely clear that it did not need to decide the meaning of "wetting agent" because "the outcome of this case does not turn on that issue." 239 F.3d at 1301. In the words of the Federal Circuit, "This case turns on whether the "admixture" limitation in claim 1 of the *'791* patent must be 'homogeneous.'" Id. The Federal Circuit held that "the admixture of diltiazem salt and wetting agent that comprises the bead of claim 1 of the *'791* patent must be homogeneous." Id, at 1302.

The wetting agent in Andrx's formulation was saccharose, which was part of a core surrounded by a mixture of diltiazem hydrochloride and other ingredients. Id., at 1299. Thus, the sugar in Andrx's bead was not admixed with diltiazem hydrochloride when the bead was manufactured. The Federal Circuit upheld the trial court's finding of non-infringement as follows:

> Biovail failed to prove by a preponderance of evidence that the "sugar" in Andrx's product forms a homogeneous admixture with diltiazem in the body. Because this finding was clearly supported by the evidence, it does not leave this court with "a definite and firm conviction that a mistake has been committed." Therefore, even assuming arguendo that "admixture" is not limited to dry state compositions and that sugar as used in Andrx's product is a "wetting agent," the district court's determination that Andrx's product does not literally infringe claim 1 of the '791 patent was not clearly erroneous.

Thus, it is absolutely clear that the trial court's definition of "wetting agent" was not relied upon by the Federal Circuit in its decision on appeal. Under the precedent set by *Masco Corp. v. United States*, the trial court's construction of the term "wetting agent" does not collaterally estop Biovail in this case.

C. As The Federal Circuit Pointed Out, But Did Not Decide, The Lower Court's Definition Of "Wetting Agent" In *Biovail v. Andrx* Was Wrong

Totally lost in TorPharm's brief is the observation by the Federal Circuit that the lower court's definition of "wetting agent" was probably incorrect. Although it stated it was not deciding the issue, it observed in a footnote that "If intrinsic evidence, including the Markush group in claim 1 and the list of wetting agents in the specification of the '791 patent unambiguously define the term "wetting agent," then the district court's reliance on expert testimony to construe this term was improper." 239 F.3d at 1301, n.1.

There can be no question that the intrinsic evidence unambiguously defines the term "wetting agent" by listing the compounds in the "Markush group." A claim construction that excludes the preferred embodiment disclosed in the specification is "rarely, if ever, correct." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583, 39 U.S.P.Q.2d 1573, 1578 (Fed. Cir. 1996). In *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1372 (Fed. Cir. 2002), the court remarked that "TorPharm's construction would

exclude the preferred embodiment (as well as all other embodiments) disclosed by the patent specifications." *Id.* The same is true here.

The description of the preferred embodiment in the '505 patent specifically includes sugars: "Among the wetting agents associated with Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified: sugars . . . ." '505 Patent, Col. 3, lines 13-16. The description of the preferred embodiment in the '791 patent is similar: "Among the wetting agents associated with Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified: saccharose, manitol, sorbitol . . . ." '791 Patent, Col. 3, lines 14-17.

In this case, TorPharm's proposed dictionary definitions of wetting agent is limited to those compounds that are "surface active agents" or "surfactants." Through its expert Dr. Goldberg, TorPharm has argued that "wetting agent" cannot include sugars, because sugars are not surface active agents. Dr. Goldberg's argument, and TorPharm's dictionary definitions, are at odds with the principle that a claim cannot be interpreted to exclude the preferred embodiment. In addition, TorPharm's arguments violate the very basic principle that a claim cannot be interpreted to exclude a definition that is set forth in the claim language itself. TorPharm's proposed definition would read "sugars" or "sugar" right out of the definition of wetting agent that is explicitly set forth in the "wherein" clauses of claim 1 of each of the '505 and '791 patents.

TorPharm argues at page 11 of its brief that on collateral estoppel principles, "at least sucrose must be excluded from the definition of sugars." This argument is preposterous. First, collateral estoppel does not apply. Second, no chemist skilled in the art would interpret the Markush group in this manner, since it is universally accepted that

"[s]ucrose is our common table sugar." ORGANIC CHEMISTRY, SECOND EDITION (Robert Thornton Morrison & Robert Neilson Boyd, ed. 1967), at p. 1025. Exhibit 6.

V. WHETHER METHYLCELLULOSE IS A SUGAR IS AN INFRINGEMENT ISSUE, NOT A CLAIM INTERPRETATION ISSUE

TorPharm devotes a substantial portion of its brief arguing that methylcellulose is not a sugar or a wetting agent. At the May 8, 2003 hearing, this Court expressed the preliminary view that the issue of whether methylcellulose is a "sugar" is an infringement issue, not a claim interpretation issue. This is not a claim interpretation issue. Conflicting expert testimony about whether methylcellulose is a "sugar" is an infringement issue.

The issue of whether methylcellulose is a sugar or wetting agent has been fully briefed on TorPharm's motion for summary judgment. In that briefing, experts for each side expressed conflicting opinions on the issue of whether methylcellulose was a sugar or wetting agent.

As is explained above, the term "wetting agent" as used in claim1 of each of the patents in suite means the compounds listed in the Markush group of each claim. "Sugar" or "sugars" or "a combination thereof" are listed among the compounds defined as wetting agents in both claims.

To summarize, and as is fully set forth in ***Biovail's Opposition To Motion For Summary Judgment Of Non-Infringement,*** and the exhibits attached thereto, Defendant's witness Dr. Goldberg testified that methylcellulose is a gum. (Goldberg Dep. at 140:24–141:1.) Dr. Goldberg also testified that a gum could be an emulsifying agent and that a gum could also be a gelling agent. (Goldberg 3/6/2003 Dep. at 41:3–8.) ***A particular component in a drug formulation can have more than one different***

function. (Goldberg 3/6/2003 Dep. at 41:18–20) For example, sometimes a gum might be an emulsifying agent but in other instances a gum might be a gelling agent. (Goldberg 3/6/2003 Dep. at :1–3) As to whether it could also be a filler, Dr. Goldberg testified that is almost becomes a matter of semantics. (Goldberg 3/6/2003 Dep. at 42:5–14.) Most often when one uses an excessive amount of a gum it is for a controlled-release product, and that function then would be controlling the release as opposed to being a filler; but at the same time, it does act as a filler. (*Id.*) Dr. Goldberg made the same point in one of his own patents, U.S. Patent No. 4,029,758, which says "It is to be appreciated that some of the ingredients enumerated herein can function in more than one capacity and therefore fall under more than one of the categories listed above. For example, calcium carbonate can function as both an opacifier and dispersant, certain starches can function as binders and as disintegrants, etc." (col. 8, lines 28–35.) So even though methycellulose is described as an excipient or a carrier in certain formulations, it can also be a wetting agent, as that term is defined by the Markush group in the claims.

Biovail's expert, Dr. Yalkowsky has submitted a declaration, relying on Dr. Goldberg's testimony that methylcellulose is a gum, that methylcellulose is a sugar because the definition of sugars includes gums. (Yalkowsky Dec. ¶ 17.) Dr. Goldberg filed a supplemental declaration, disavowing his prior deposition testimony.

This is not a claim interpretation issue. It is an issue that must be resolved by the jury, who must resolve the conflicting testimony of experts.

VI. THE PHRASE "MAINTAIN THE SOLUBILITY . . ."

The phrase in claim 1 of the '791 patent, "to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will

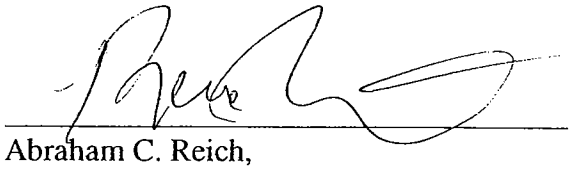
meet therein," means that Diltiazem is in solution within the membrane of the coated bead so that it can be released through the membrane as the membrane-coated bead travels through the entire length of the gastrointestinal tract, and the release of diltiazem is unaffected within the tolerances disclosed in the patent by the presence or absence of food. This interpretation is supported by the specification of the patent, which explains that the formulation is free from a "food effect." "The product . . . given with food is bioequivalent to the administration without food." '791 Patent, Col. 8, lines 40-42. Thus, the release of diltiazem from the microcapsules of the invention is not materially affected by the differences in pH (described in Exhibit 3) as the microcapsules pass through the GI tract.

VII. CONCLUSION

For the reasons set forth above, Biovail respectfully submits that this Court should find that the term "wetting agent" in claim 1 of each of the patents in suit is defined by the Markush group in each claim.

Biovail also submits that the phrase "to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein" means that Diltiazem is in solution within the membrane of the coated bead so that it can be released through the membrane as the membrane-coated bead travels through the entire length of the gastrointestinal tract, and the release of diltiazem is

unaffected within the tolerances disclosed in the patent by the presence or absence of food.



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Dated: June 2, 2003